Reviewer’s report

Title: Preparing for the unexpected: Special considerations and complications after sugammadex administration

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Reviewer: Aaron Kopman

Reviewer’s report:

The literature on sugammadex is now so massive that any review article about this drug must have limited goals. The Introduction Section ("Background" page 5) must explain that this review is focused on aspects of the clinical use of sugammadex that are controversial or may require special attention. A brief outline of the topics to be covered at the outset would be very helpful.

Page 5, lines 2-9: This section needs a total rewrite. The sentence beginning "As sugammadex is most commonly..." is confusing and adds nothing of value to the introduction. Delete. Ditto the sentence mentioning "new opportunities and challenges." What opportunities? What challenges? Etc. Ditto, the comment re "best clinical practices." Most of this introduction is composed of elaborate language saying nothing. Keep it simple.

Sugammadex is now a well understood drug. Thus I question the necessity of including the section entitled "Characterizes and Clinical use of Sugammadex." (Page 5, line 13 thru Page 614). Delete.

The Section on Recurrence of Neuromuscular Block (pages 7-8): This section should begin by noting that recurrence of block post sugammadex administration has been observed. Give examples. Only then should possible mechanisms be discussed. While administering sugammadex based on actual body weight in the obese has been recommended, this may be unnecessarily expensive. Van Lanker (ref #69) suggest 140% of ideal body weight (IBW). Sanfillippo (ref # 70) argues that doses based on IBW may be adequate.

This section of the manuscript is meant to deal with the issue of recurarization however refs #s 7, 8, 9 and 13 do not deal with this occurrence. References 10-12 are more to the point. It should be noted that in refs 10 and 12 clearly inadequate doses of sugammadex were delivered and the degree of "recurarization" was modest indeed. Reference #11 is the only case I can find describing clinically serious recurarization post sugammadex. In fact this case is so unique that one must wonder if the intra-op neuromuscular monitoring (kinemyography) was accurate.

I must take issue with the authors’ comment on page 8, line 14. Certainly, objective neuromuscular monitoring is optimal. Nevertheless, if the manufacturers' recommendations re sugammadex dosage are followed (dose based on TOF-count or post-tetanic count at the adductor pollicis) I see no reason why qualitative monitoring is not sufficient. It must be
remembered that these doses were intended to work for vecuronium as well as rocuronium, a more difficult drug to reverse.

Planned Re-establishment of Neuromuscular Blockade after Sugammadex Administration.


Hypersensitivity/Allergy

Testing for and treatment of sugammadex induced allergy/anaphylaxis is no different from other allergens e.g. rocuronium. Hence, I'm not sure that lines 7 - 16 on page 13 are necessary.

Bleeding Time Etc.

Put this in a historical perspective. Initial in vitro observations suggested that sugammadex in high doses mildly elevated the PT and APTT. Subsequent clinical studies have not confirmed that sugammadex is associated with any risk of peri-operative bleeding.

The Obese Patient

The statement (page 19, lines 8-9) that sugammadex should be dosed on actual not ideal body weight is not universally agreed upon. Yes, using actual body weight is the most conservative approach, certainly there are advocates of that approach (see ref #71), unfortunately this has potentially less than desirable economic consequences. There is considerable opinion that dosage of this magnitude is not required. See references #69 and 70. Loupec et al (ref #9) report that "In morbidly obese patients, 4 mg/kg of ideal body weight of sugammadex allows suitable reversal of deep rocuronium-induced neuromuscular blockade. Monitoring remains essential to detect residual curarisation or recurarization." Similarly Abd El-Rahman et al. [Comparison of three different doses sugammadex based on ideal body weight for reversal of moderate rocuronium-induced neuromuscular block in laparoscopic bariatric surgery. Minerva Anestesiol. 2017; 83:138-144] concluded that "sugammadex 1.5 mg/kg calculated according to IBW successfully reversed moderate rocuronium-induced neuromuscular block in laparoscopic bariatric surgeries." Finally, Badaoui et al [Reversal of neuromuscular blockade by sugammadex in laparoscopic bariatric surgery: In support of dose reduction. Anaesth Crit Care Pain Med. 2016; 35:25-9] suggest a dose based on IBW plus 35-50% quite similar to the recommendations of Van Lancker (ref #69).
Bottom line: This is still an area of controversy. If sugammadex were inexpensive opting to base doses on actual body weight would seem reasonable. At about $90 for a 200 mg vial acquisition costs must be a consideration.

Renal Impairment:

What are the authors recommendations in ESRD. Do they recommend avoiding sugammadex? They never say.

Cost:

Page 25 line 15 thru page 26 line 3: It is true that that total paralysis time from rocuronium 1.2 mg/kg followed 3 min later by sugammadex 16 mg/kg is slightly shorter than the duration of effect of succinylcholine 1.0 mg/kg. To imply that this is "cost effective" makes defies logic. The proposition that reversal with sugammadex in CICV situations is a potential life-saver compared to succinylcholine has yet to be proven. In fact, a convincing argument can be made that "rescue reversal" is largely a myth. See Naguib et al. [The Myth of Rescue Reversal in "Can't Intubate, Can't Ventilate" Scenarios. Anesth Analg 2016: 123:82-92].

Page 26, lines 5-7. This is not exactly what happened. Neostigmine was one of a large number of "grandfathered" drugs whose use anteceded the FDA approval process. About a decade ago, in an attempt to get some control over these compounds the FDA introduced a greatly accelerated and relatively inexpensive approval protocol for these old drugs. Eclat Pharmaceuticals took advantage of this process, received FDA approval, applied for and received a "brand name" and promptly raised the price of neostigmine by an order of magnitude. Once Eclat had FDA approval they then petitioned the FDA to remove all competing generic formulations from the drug distribution chain. The Agency complied.

Currently in the USA a case can be made that sugammadex reversal is cost competitive with neostigmine-glycopyrrolate. However, this is probably not true for much of the world where neostigmine remains quite inexpensive.

Conclusions: Page 27, line 2. While it is hard to argue against the virtues of objective neuromuscular monitoring, in an environment in which sugammadex is readily available I would maintain that mandatory use of a conventional peripheral nerve stimulator is sufficient. Yes, the depth of neuromuscular block is necessary information if sugammadex is to be used rationally and safely. However, once the subjective TOF-count or post-tetanic count is known if the manufacturer's dose recommendations are followed, I would suspect that inadequate neuromuscular recovery must be very rare indeed.

Table 1. Delete.

List of Abbreviations: This should precede the Introduction.
Figure 3: None of this is unique to hypersensitivity to sugammadex. Delete.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

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